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EDITORIAL COMMENT

Non–ST-Segment Elevation Myocardial Infarction

Revascularization for Everyone?*

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Patients with acute coronary syndrome, the sudden clinical manifestation of atherosclerotic heart disease, may present as ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina. Patients with STEMI typically have complete and persistent occlusion of a large epicardial coronary artery with a large area of myocardium at risk and severe chest pain, whereas patients with NSTEMI may present with a more heterogeneous condition: varying degrees of reduction of coronary flow but without complete coronary occlusion in combination with distal embolization of thrombotic material and accompanying coronary spasm. Atherosclerotic changes in the vessel wall, extent of calcification, the degree of plaque rupture and subsequent intracoronary thrombus formation may vary considerably in NSTEMI patients. In addition, myocardial necrosis (and troponin elevation) may occur in the absence of coronary thrombosis but in the presence of stable but diffuse severe coronary disease and clinical conditions that increase myocardial demand, such as acute decompensated heart failure or tachyarrhythmias, such as rapid atrial fibrillation. Patients with NSTEMI have lower 30-day mortality than STEMI patients, but at 1 year, this difference in mortality is no longer present.

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Current STEMI guidelines recommend urgent angiography followed by immediate mechanical opening of the infarct-related coronary artery to restore coronary flow (reperfusion therapy), a strategy that has been shown to reduce mortality. In NSTEMI patients, however, there has been continued debate over the last 10 years whether "immediate," "urgent," or "early" angiography and revascularization is beneficial compared with a more "conservative" or "selective invasive" approach.

Current NSTEMI guidelines recommend the assessment of ischemic risk and bleeding risk using validated risk scores in each individual patient to decide on pharmacological and invasive management (1,2). The guidelines recommend urgent or immediate transfer to the catheterization laboratory for patients with ongoing signs and symptoms of ischemia and for patients with hemodynamic or electric instability. An early invasive management in high-risk patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) is recommended, with high-risk features, including evidence of myocardial necrosis resulting in troponin elevations, ongoing myocardial ischemia with dynamic ST-segment changes on the electrocardiogram, the presence of diabetes mellitus, and a history of a recent percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Although women and elderly patients are under-represented in the randomized controlled trials (RCT) and these patients may be at higher risk of procedural complications, available evidence suggest that after appropriate risk stratification, the benefit of an early invasive management extends to all subgroups. Importantly, with advanced age, the absolute risk of death or MI is increased and potential absolute risk reduction from early revascularization in elderly patients may be substantial (1,2).

Meta-analyses of the RCT comparing an early invasive management strategy with a more conservative or selective invasive management have shown that an early invasive management reduced the composite of death or MI, in particular in patients with high ischemic risk scores (3,4). In a recent analysis, including FIR (FRISC-II [Fragmin and Fast Revascularization During Instability in Coronary Artery Disease], ICTUS [Invasive Versus Conservative Treatment in Unstable Coronary Syndromes], and RITA 3 [Randomized Intervention Trial of Unstable Angina]), of a large per patient combined dataset, comprising over 5,000 patients, 5-year incidence of the combined endpoint death or nonfatal MI was reduced by an early invasive management (5). Yet, in contrast to the evidence from STEMI trials, neither in the meta-analyses of all RCT nor in the FIR analysis has a statistically significant reduction in long-term mortality been demonstrated to be associated with early invasive management. In the analysis by Mehta et al. (3), combining the results of 7 trials with varying time intervals of follow-up, mortality associated with a routine invasive management at the end of follow-up was 5.5% versus 6.0% associated with a conservative management (odds ratio [OR]: 0.92; 95% confidence interval [CI]: 0.77 to 1.09; $p = 0.34$). In the FIR analysis, comprising 5,467 patients with 5-year outcomes, a trend toward a reduction in cardiovascular deaths and in all deaths was shown in favor of an early invasive management compared with a more

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selective invasive management (cardiovascular death: RI 6.8% vs. SI 8.1%; hazard ratio [HR]: 0.83, 95% CI: 0.68 to 1.01; p = 0.068) (all deaths: routine invasive [RI] 10.6% vs. selective invasive [SI] 11.7%; HR: 0.90, 95% CI: 0.77 to 1.05). For the combined endpoint, there were 2.0% to 3.8% absolute reductions in cardiovascular death or MI in the low- and intermediate-risk groups and an 11.1% absolute risk reduction in highest-risk patients (5).

In this issue of *JACC: Cardiovascular Interventions*, Puymirat et al. (6) provide data for a large cohort of NSTEMI patients from the FAST-MI (French Registry of Acute Coronary Syndrome). During 1 month in 2005, 3,670 all-comers ACS patients were prospectively enrolled in 223 centers within 48 h after symptom onset, including 1,645 NSTEMI patients (45%). Invasive management strategy (IS) was defined as angiography with or without revascularization, and conservatively managed patients (CS) did not undergo angiography and received only medical therapy. Management choice was at the discretion of the treating physician, resulting in 80% of patients managed invasively. Patients in the IS group were younger (67 ± 12 years vs. 80 ± 11 years), less often women (29% vs. 51%), and had a lower GRACE (Global Registry of Acute Coronary Events) risk scores (137 ± 36 vs. 178 ± 34) compared with patients treated with CS. In-hospital mortality was significantly more frequent in patients with CS than with IS (13.1% vs. 2.0%). Use of IS was statistically significantly associated with a lower 3-year all-cause and cardiovascular mortality (17% vs. 60% and 8% vs. 36%). After propensity score matching (181 patients per group) to adjust for differences in baseline risk, 3-year survival was significantly better in patients treated with an invasive strategy. The study has several important strengths and adds to our knowledge from RCT and meta-analyses. First, all-comers patients were included in a real-life clinical environment. Second, the study excluded patients with iatrogenic or procedure-related MI, as well as patients in whom another diagnosis was favored over ACS and patients with negative cardiac necrosis markers. Third, the registry was a prospective registry, patients were followed up for 3 years, and importantly, follow-up was 99% complete at 1 year and 97% at 3 years. In addition, bleeding complications and need for blood transfusions were carefully recorded. Registry data without scheduled follow-up visits and formalized event monitoring may be limited by underreporting of ischemic events and (repeat) revascularization procedures, but vital status and cause of death is likely to be reliable and complete in this study. Can we now conclude that an early invasive strategy in all NSTEMI patients reduces mortality and restrict a conservative strategy only to patients who are considered low risk, too high risk to undergo a procedure, or who are unwilling to undergo angiography?

Perhaps not. In a post hoc analysis of the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and glycoprotein IIb/IIIa Inhibitors) trial, one-third of patients with NSTE-ACS and significant coronary disease on early angiography were managed without in-hospital revascularization. The strongest independent predictors of conservative medical management versus any intervention were prior CABG, lower body weight, and 3-vessel disease, clearly delineating increased baseline risk. With conservative medical management, the cumulative risk of 1-year mortality after discharge increased during the first 90 days and thereafter remained higher at 7.7% compared with that seen in patients treated with PCI (3.6%) or CABG (6.2%) (7). This association between angiography and a reduction in mortality in non-STE-ACS patients has also been consistently shown in retrospective cohort studies (8). Typically, a relative risk reduction of 50% in cardiovascular death or all-cause death was associated with early angiography, but baseline risk was also significantly higher in conservatively managed patients. In registry cohort studies, where the decision to perform angiography is not formally defined in the protocol, strategy is dependent on the availability of a catheterization laboratory, hospital protocols, regional practice, and individual physician preference. Thus, if angiography is the default strategy in patients with NSTEMI, the decision to refrain from angiography is likely reached on the basis of actual or anticipated individual patient risk associated with an invasive procedure, such as severe renal insufficiency, severe chronic heart failure, pulmonary disease, absence of revascularization options in patients with recent angiographic data, or frailty associated with advanced age. The clinical information available to the treating physician will not be completely captured in the variables defined in the registry report form. Analytical techniques to eliminate bias due to confounding, such as propensity score analyses may not be able to adjust for important prognostic indicators associated with the decision not to perform angiography. To illustrate this, Hirsch et al. (9) recently performed a "retrospective" analysis of patients in the ICTUS study and demonstrated a 41% reduction in mortality associated with revascularization, whereas in the same dataset, prospective randomization to an invasive management strategy was not shown to be beneficial. Stukel et al. (10) have previously shown that the observational association of invasive practice and outcome in acute MI patients was highly dependent on the statistical methods used. Propensity score adjusted analyses will inevitably suffer from residual unmeasured confounders, whereas other techniques, such as instrumental variable analyses designed to control for hidden bias, will not. Thus, as Puymirat et al. (6) mentioned, the results of their analyses are intriguing but can only be considered indicative. The use of Kaplan-Meier curves in Figure 1 of the Puymirat et al. (6) paper suggests that the management strategy (IS or CS) was

chosen at hospital admission (time 0 in the Kaplan-Meier curve). However, the CS group consisted of all patients who did not undergo coronary angiogram during the initial hospitalization, including patients who died early, that is, before they could be catheterized. This analytical approach biases survival in the IS group.

Finally, the results from the RCT represent clinical practice from the era before 2005. In addition, Puymirat et al. (6) enrolled patients in 2005, and both the diagnostic and therapeutic treatment options for ACS patients have evolved dramatically since then. The use of the new $P2Y_{12}$ antagonists (e.g., prasugrel and ticagrelor) was associated with an approximately 20% relative reduction in ischemic events in ACS patients and improved prognoses in STEMI and NSTEMI patients alike, both with an invasive management and with medical management. Bleeding was also reduced using Fondaparinux or bivalirudin (1,2). Since 2005, we have better PCI techniques and better coronary stents with improved deliverability, lower restenosis risk, and lower stent thrombosis risk. Access site–related bleeding complications decrease using the radial approach. With better tools for risk stratification, we are able to identify ACS patients who may benefit most from early angiography and revascularization. Physicians are struggling with the clinical implications of the high-sensitivity troponin assays, which allow us to detect even the smallest changes in cardiac troponins, which inevitably results in a larger number of patients with ACS who, according to the guidelines, should be managed invasively.

In summary, early intervention is recommended in high-risk ACS patients and implemented in most centers. Although mortality reduction may be modest, an invasive strategy significantly reduced death or MI. Early angiography is safe and practical in most patients. Yet, perhaps it is time for a new, large, randomized clinical trial for intermediate-risk NSTE-ACS patients, comparing an early invasive strategy with a selective invasive strategy, and using high-sensitive troponin measurements and risk stratification tools, the latest interventional modalities, and optimized pharmacological standards of care. The outcome of such a trial, which could enroll a representative number of elderly and female patients to mirror our everyday clinical patient population, might surprise us.

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